

Application Serial No. 09/654,276  
Amendment dated April 8, 2005  
Reply to Office Action of December 8, 2004

### REMARKS

Applicant has read and considered the Office Action dated December 8, 2004 and the references cited therein.

Applicant respectfully requests reconsideration of the claims in view of the remarks provided herein. Claims 1-3, 5, 6, 9, 10, and 16-24 are currently pending.

### Specification

The Examiner objected to legal phraseology in the abstract. Applicant has amended the abstract as required by the Examiner. Withdrawal of this objection is respectfully requested.

### 35 U.S.C. § 103

Claims 1-3, 5, 6, 9, 10, and 16-24 were rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 6,099,832 (Mickle et al.) in view of WO97/44070 (Shapiro et al.). The Action alleges that it would have been obvious to substitute the alginate scaffolds disclosed in Shapiro et al. for the collagen scaffolds taught by Mickle et al. in the methods of treating damaged cardiac tissue taught by Mickle et al. Applicant respectfully traverses the rejection.

The Patent Office bears the initial burden of factually supporting any *prima facie* conclusion of obviousness. MPEP § 2142. Three criteria must be to establish a *prima facie* case of obviousness. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991). One or more of the three criteria has not been established.

Mickle et al. does not teach or suggest using a polysaccharide scaffold. Mickle et al. suggest transplanting biodegradable or non-biodegradable scaffolds seeded with cells. The transplant used by Mickle et al., however, was only a suspension of cells in culture medium and not a polymeric scaffold seeded with cells. See, for example, Mickle et al. at:

column 13, lines 47-56

Cultured cells were washed three times with phosphate buffered saline to remove dead cells and then detached from the cell culture dish and each other with 0.05% trypsin in phosphate buffered saline for 3 minutes. After adding 10 ml of cultured medium, the cell suspension was centrifuged at 580xg for 3 minutes. The cell

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pellet was resuspended in culture medium at a concentration of  $4 \times 10^6$  cells/ml culture medium. The volume of cell suspension was 0.25 ml for each cell transplantation. (emphasis added)

column 13, lines 61-63

The cell suspension (0.25 ml) was injected into the scar tissue of the animals of the transplant group using a tuberculin syringe. (emphasis added)

Mickle et al. does not teach that the results achieved with injection of cells could be achieved with polymeric grafts seeded with such cells. When referring to the results, Mickle et al. discuss the optimal time for "cell transplantation" (col. 19, line 6) and describe the cell transplantation and results immediately thereafter (col. 19, line 23). Furthermore, Figure 1 describes cardiac function after cell transplantation.

Mickle et al. failed to show beneficial effect of collagen biograft implantation on cardiac developed pressure, which reflects left ventricular contractility. In contrast, the present application shows that alginate biograft implantation prevents left ventricular contractility deterioration, as reflected by preservation of fractional shortening after implantation. Moreover, in control animals there was significant deterioration in LV performance, as shown by the deterioration of fractional shortening.

In a subsequent publication (Li et al., 1999, *Circulation*, II-63 - II-69; copy enclosed), the group of Mickle et al. teaches that transplantation of gelatin-seeded grafts does not improve ventricular function. Li et al. describe the preparation of cell-seeded Gelfoam grafts (absorbable gelatin, Pharmacia & Upjohn) (II-64) and their implantation into injured hearts of rats by suturing to the surface of the myocardial scar. As shown in Fig. 7 and stated by the authors:

Left ventricular developed pressure, over a range of intraventricular balloon volumes, was best preserved in the sham-operated animals (Figure 7). Rats in which the cell-seeded grafts had been sutured to the myocardial scar tended to have slightly better ventricular function than rats with unseeded grafts, but the differences were not statistically significant. (paragraph bridging II-66 and II-67).

Furthermore, "grafts implanted into subcutaneous tissue maintained spontaneous and rhythmic contractility, but the effect of this graft on ventricular function after myocardial scarring remains

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uncertain" (II-69, right hand column, in Conclusions). Thus, transplantation of the gelatin-seeded grafts did not improve left ventricular function.

In contrast, the present application shows that transplantation of cell-seeded alginate grafts into damaged hearts improves cardiac function. As described in Example 8 of the present application: "... in the biograft-treated rats, attenuation of all LV remodeling indices was observed (Table 1B). During the follow-up period, there was no significant change in LV internal diastolic and systolic diameters ...etc.".

In view of the forgoing, Mickle et al. would not have motivated one of skill in the art to use the scaffolds of Shapiro et al. with the cardiomyocytes and growth factors of Mickle et al. to treat damaged myocardium. As evidenced by Li et al., one of skill in the art would not have expected the alginate scaffolds of Shapiro et al. to be useful in the methods taught by Mickle et al. As shown by the later work of Mickle et al., transplantation of gelatin-seeded grafts did not improve left ventricular function. Therefore, one of skill in the art would not have been motivated to improve ventricular function or treat damaged myocardium by transplantation of cell-seeded polymeric grafts.

Accordingly, Applicant submits that a *prima facie* case of obviousness has not been established. Withdrawal of the rejection is respectfully requested.

#### Conclusion

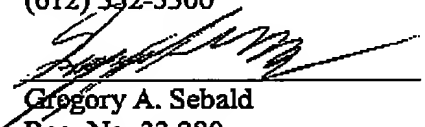
In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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Date: April 8, 2005



  
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